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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/040,244	10/26/2001	Walker R. Force	P 021286 0272501	9259

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/040,244	FORCE ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11,20-28,30 and 31* is/are pending in the application.

4a) Of the above claim(s) *22-28 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11,20,21 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed has7/28/05 been entered.
Claims 1-7, 12-19 and 29 have been canceled.
Claim 31 has been added.

Claims 8-11, 20-28 and 30-31 are pending.

Claims 8-11, 20-21 and 31 are under consideration in the instant application.

Claims 22-28 and 30 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to nonelected inventions.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 7/28/05.
The rejections of record can be found in the previous Office Action.

3. Upon the cancellation of claims 4-7, 14-15 and, 17-20, the previous rejections under 35 U.S.C. 112, first and second paragraphs, have been obviated.

4. New Ground of Rejection

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It has been well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It has been known that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen-binding sites.

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 79: 1979-1983, 1982; see entire document, including the Abstract).

Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Further, Colman (Research in Immunology 145: 3-36, 1994) describes the confusing picture of the specificity of the antibody-antigen interactions in that in one structural context, a very conservative substitution may abolish binding; yet in another non-conservative substitution may have very little effect on the binding affinity (see entire document, including page 35, "Structural context and repertoire size").

The specification provides insufficient direction or guidance regarding how to modify the antibody or functional fragment to include one or more amino acid substitutions or additions to retain substantially the same binding specificity of the anti-human CD40 antibody or functional fragment.

It is also noted that the claims do not recite a base amino acid sequence or structure nor a source such as a particular hybridoma for the claimed anti-CD40 antibodies. Applicant has not provided sufficient biochemical information, such as the sequence information or as providing the hybridomas for the claimed anti-CD40 antibodies that may enable a skilled artisan to modify a known anti-CD40 antibody with any addition, deletion or substitution, as broadly encompassed by the claimed invention.

Given the well known polymorphism of antibodies (as evidenced by page 35, "Structural context and repertoire size" of Colman, Research in Immunology 145: 3-36, 1994);
it would have been undue experimentation to make and use the vast repertoire of amino acid modifications to enable the scope of the functional anti-CD40 antibodies encompassed by the claimed invention.

Without sufficient guidance and given the well known complexity and unpredictability of modifying amino acids encoding an antibody as well the well known polymorphism of antibodies; it would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use the vast repertoire of amino acid modifications in order to make and use the antagonistic anti-CD40 antibodies, broadly encompassed by the claimed invention.

5. Claims 8-11, 20-21 and 31 are rejected under 35 U.S.C. § 102(e) as being anticipated de Boer (U.S. Patent No. 5,874,082) (1449; #DR) (see entire document) essentially for the reasons of record.

Applicant's arguments, filed 7/28/05, have been fully considered but are not found convincing essentially for the reasons of record.

As pointed out previously, the products of the instant claims and the prior art are defined in terms of certain functional characteristics.
Also, comparison of the instant products with prior art is difficult since the Office is not equipped to manufacture the claimed product and/or prior art products that appear to be related and conduct comparisons.

Applicant's reliance upon the comparison of the prior art antagonistic 5D12 CD40-specific antibody with the instant Example 6, pages 68-70 and Figure 10 of the instant specification is acknowledged.

However these comparisons and results were derived under certain assay conditions.

In contrast to applicant's observations with the 5D12 antibody,
Example 5 on columns 18-19 of de Boer do teach:
"Very potent inhibition occurred. At concentrations as low as 10 ng/ml each, the three anti-CD40 mAbs 5D12, 3C6 and 3A8 inhibited B cell proliferation completely. Half-maximal inhibition was found at about 1 ng/ml."

Therefore, the inhibition taught by the reference does anticipate the claimed limitations as they read on inhibiting B cell proliferation when the concentration of the antibody is in the range of 0.1 µg /ml to 10 µg/ml, as encompassed by the instant claims.

Given the properties of both agonistic and antagonistic anti-CD40 antibodies, including a number of binding and functional assays taught by de Boer, the claimed binding and functional properties of anti-CD40 antibodies would have inherent properties associated with said agonistic and antagonistic taught by the prior art.

Applicant's arguments are not persuasive.

As indicated previously,
De Boer et al. teach both agonistic and antagonistic anti-CD40 antibodies (see entire document). De Boer disclose that all anti-CD40 known in the art have a stimulatory effect on B cells (column 2, paragraph 3) and teach antagonistic anti-CD40 antibodies (see Summary of the Invention, Detailed Description of the Invention and Claims). De Boer et al. teach that recombinant forms of antibodies and antibody fragments as well as pharmaceutical compositions thereof can be used for a variety of procedures (see Detailed Description, particularly columns 5-10). De Boer et al. teach a variety of assays to test anti-CD40 antibodies (e.g. B cell proliferation assay, B cell activation assay, immunoglobulin quantification) (see entire document) and that CD40 epitopes can be identified (see column 7, paragraph 4 - column 8, paragraph 2).

The products of the instant claims and the prior art are defined in terms of certain functional characteristics. Comparison of the instant products with prior art is difficult since the Office is not equipped to manufacture the claimed product and/or prior art products that appear to be related and conduct comparisons. Given the properties of antagonistic anti-CD40 antibodies, including a number of binding and functional assays taught by de Boer, the claimed binding and functional properties of anti-CD40 antibodies would have inherent properties associated with said antagonistic taught by the prior art. Given the teachings of recombinant antibodies, the ordinary artisan would have immediately envisaged that anti-CD40 antibodies would have had differences in amino acids from one another and thereby anticipating the modifications encompassed by newly added claim 31.

Applicant's arguments have not been found persuasive.

6. Claims 8-11, 20-21 and 31 are rejected under 35 U.S.C. § 102(e) as being anticipated Siegall (US 2004/0235074 A1) (see entire document) essentially for the reasons of record.

Applicant's arguments, filed 7/28/05, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same as they rely upon the prior art teaching, in part, the antagonistic 5D12 antibody.

As pointed out above, and
in contrast to applicant's observations with the 5D12 antibody,
Example 5 on columns 18-19 of de Boer et al. above do teach:
"Very potent inhibition occurred. At concentrations as low as 10 ng/ml each, the three anti-CD40 mAbs 5D12, 3C6 and 3A8 inhibited B cell proliferation completely. Half-maximal inhibition was found at about 1 ng/ml."

Therefore, the inhibition taught by the reference does anticipate the claimed limitations as they read on inhibiting B cell proliferation when the concentration of the antibody is in the range of 0.1 µg /ml to 10 µg/ml, as encompassed by the instant claims.

Given the properties of both agonistic and antagonistic anti-CD40 antibodies, including a number of binding and functional assays taught by de Boer, the claimed binding and functional properties of anti-CD40 antibodies would have inherent properties associated with said agonistic and antagonistic taught by the prior art.

As previously taught, Siegall et al. teach classes of both agonistic and antagonistic anti-CD40 antibodies (see entire document, including Section 2.2. Anti-CD40 Antibodies in the Background of the Invention; Summary of the Invention and Detailed Description of the Invention). In addition, Siegall et al. teach recombinant antibodies and fragments thereof (see Antibody Derivatives in Section 5.6, particularly paragraphs [0077] – [0091]) as well as Formulations (See Section 5.9.2, particularly paragraph [0122] – [0133]). In addition, Siegall et al. exemplify various assays to study the test anti-CD40 antibodies (see Examples).

The products of the instant claims and the prior art are defined in terms of certain functional characteristics. Comparison of the instant products with prior art is difficult since the Office is not equipped to manufacture the claimed product and/or prior art products that appear to be related and conduct comparisons. Given the properties of both agonistic and antagonistic anti-CD40 antibodies, including a number of binding and functional assays taught by Siegall et al., the claimed binding and functional properties of anti-CD40 antibodies would have inherent properties associated with said agonistic and antagonistic taught by the prior art. Given the teachings of recombinant antibodies, the ordinary artisan would have immediately envisaged that anti-CD40 antibodies would have had differences in amino acids from one another and thereby anticipating the modifications encompassed by newly added claim 31.

Applicant's arguments have not been found persuasive.

7. Upon reconsideration of applicant's arguments, the previous rejection under 35 U.S.C. § 102(b) as being anticipated by Ahuja et al. (U.S. Patent No. 6,482,411) (1449; #DR) has been withdrawn.

8. Claims 8-11, 20-21 and 31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 6, 8, 23-26 and 65-71 of copending application USSN 09/844,684. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to the same or nearly the same anti-CD40 antibodies. Although the instant claims do not recite cell lines or hybridomas expressing said antibodies, such cell lines expressing antibodies were well known and practiced in the antibody art either in the producing of said antibodies (e.g. monoclonal antibody technology or recombinant antibody technology) at the time the invention was made. Although, the copending claims are drawn to human antibodies and the instant claims do not recite human antibodies per se, it was well practiced and known by the ordinary artisan to employ various antibody forms, including human antibodies in clinical practice. In addition to the interacting with human cell receptors and interactions, human antibodies had the well known advantage of being less immunogenic and of having an increased half-life in human patients.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Given the absence of additional rebuttal to the outstanding rejection of record in applicant's amendment, filed 7/28/05, it appears that applicant has acquiesced to the double patenting rejection of record.

The rejection is maintained for the reasons of record.

9. No claim allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
October 17, 2005